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# **The effect of safety warnings on antipsychotic drug prescribing in elderly persons with dementia in the United Kingdom and Italy: a population-based study**

Janet Sultana, Andrea Fontana, Francesco Giorganni, Alessandro Pasqua, Claudio Cricelli, Edoardo Spina, Giovanni Gambassi, Jelena Ivanovic, Carmen Ferrajolo, Mariam Molokhia, Clive Ballard, Samantha Sharp, Miriam Sturkenboom, Gianluca Trifirò

## **Appendices**

# Appendix 1: European studies carried out investigating the effect of drug safety warnings on antipsychotic use in older people.

Author, year	Setting	Population	Exposure	Outcomes	Findings
Gallini et al., 2014	EGB database (France)	Elderly patients with and without dementia	All APs, APs by class and olanzapine and risperidone individually from 2003 to 2011	Monthly prevalence of AP use as a function of the 2004 and 2009 EMA warnings	<ul style="list-style-type: none"> <li>-The monthly use of all APs decreased steadily from 2003-2011 from 16-11% and did not appear to be associated with the warnings.</li> <li>-Atypical APs decreased from 12% in 2003 to 5% in 2011 but the trend was already decreasing before the warning; after the 2009 warning this decrease stopped.</li> <li>-Conventional AP use increased from 3% in 2003 to 5% in 2011. Minimal changes in drug utilization were seen after both warnings.</li> <li>-Olanzapine use remained stable at 0.5% from 2003-2011; no change in trend was seen after the warnings.</li> <li>-Risperidone use increased from 2% in 2003 to 4% in 2011; use of this drug increased slightly after the 2004 warnings and decreased slightly after the 2009 warning.</li> </ul>
Schulze et al., 2013	GEK database (Germany)	Elderly dementia patients	All APs and APs by class from 2004 to 2009	Change in yearly prevalence of AP use, number of AP packages and DDD per person per year as a function of the 2004 drug safety mails in Germany, the 2005 FDA safety warning on atypical AP use and the 2008 FDA/EMA warning on conventional AP use.	<ul style="list-style-type: none"> <li>-The yearly prevalence of any AP use changed minimally after the 2004 warning (from 35% before to 34% the year after). Similarly small changes were seen after the 2005 warning, where the prevalence of use changed from 34% to 32% in the year after. No changes were seen after the 2008 warning, with the prevalence remaining stable at 32%.</li> <li>-The trend for conventional AP use was very similar to that of AP use overall, starting at 27% before to 26% after the 2004 warning, decreasing to 23% after the 2005 warning. The prevalence of use remained at 23 % before and after the 2008 warning.</li> <li>-The yearly prevalence of atypical AP use remained relatively constant at 17-18% over the observation period.</li> </ul>
Guthrie et al., 2013	PCCIU database (Scotland)	Elderly dementia patients	All APs and risperidone, olanzapine, quetiapine individually from 2001–2011	Quarterly prevalence of oral AP prescribing, initiation and discontinuation; prescription of hypnotics, anxiolytics or antidepressants	<ul style="list-style-type: none"> <li>-In 2001 15% of dementia patients were prescribed any oral AP, increasing to 23% just before the 2004 warning. Levels dropped back to 15% after the 2004 warning. The 2009 warning was associated with a reduction from 17% to 14% after the 2009 warning.</li> <li>-Risperidone use decreased from 12% before the 2004 warning to 4% shortly after. No decrease was seen after the 2009 warning.</li> <li>-Olanzapine use decreased from 3% before the 2004 warning to 1% shortly after. No change was seen after the 2009 warning.</li> <li>-Quetiapine use increased steadily after the 2004 warning, up to a peak of 8% just before the 2009 warning. There was a short-term decrease in quetiapine use after the 2009 warning which decreased back to pre-warning levels within 1 year.</li> </ul>
Franchi et al., 2012	Lombardy Region Drug Administrative Database (Italy)	Elderly dementia patients treated with AChEIs	All APs, APs by class and olanzapine, quetiapine, haloperidol, clonazepam and risperidone individually from 2002 to 2008	Number of AP prescriptions per person and gap between AP prescriptions as a function of the 2004 EMA warning and the 2006 AIFA warning; yearly prevalence of AP use, probability of continuing antipsychotic treatment.	<ul style="list-style-type: none"> <li>-The yearly prevalence of AP use decreased from 23% before the 2004 warning to 17% a year after the 2004 warning. AP use decreased from 17% to 16% after the 2006 warning but levels rose back up to 17% 1 year later.</li> <li>-Atypical AP use decreased from 20% before the 2004 warning to 16% in the year after. Following the 2006 warning, atypical AP use decreased from 16% to 14% within a year but rose back to 15% the year later.</li> <li>-Conventional AP use decreased slightly following the 2004 warning, from 4% to 3% over 2 years. Levels rose to almost 5% after the second warning in 2006.</li> <li>-Olanzapine use decreased from 5% to 3% within a year of the 2004 warning but no change was seen after the 2006 warning.</li> <li>-Risperidone use was very similar to olanzapine but levels decreased by approximately 1% after the 2006 warning.</li> <li>-Quetiapine use was already increasing before the 2004 warning and continued to do so after, albeit at a lower rate (from 9% before to 11% a year after). After the 2006 warning, there was a short-term decrease in use from 13% to 10% after a year, which rose to 12% a year later.</li> <li>-The use of haloperidol did not seem to change with the warnings, the prevalence of which remained below 2% from until 2007, increasing to 3% in 2008.</li> </ul>

Trifiró et al, 2010	HSD-CSD LPD Italian nationwide database	General population, elderly persons and elderly persons with dementia	AP use by class, and by individual APs (haloperidol, promazine, quetiapine, chlorpromazine, risperidone, olanzapine, clotiapine and thioridazine) among elderly persons with dementia from 2000 to 2005.	One-year and monthly prevalence of AP use as a function of the 2004 MHRA warning and the 2005 FDA warning.	-The monthly prevalence of conventional AP use increased from 12% to 14% after the 2004 warning and did not appear to change after the 2005 warning. - The monthly prevalence of atypical AP use decreased from 8% to 6% after the 2004 warning but started increasing again after the 2004 warning.
Sanfeliix-Gimeno et al., 2009	Valencia Health Agency pharmacy claims database (Spain)	Elderly patients and younger adults	Risperidone and olanzapine use (stratified by strength) from 2000 to 2006	Monthly prevalence of risperidone and olanzapine use in DDD as a function of three warnings issued by the Spanish drug agency: March and May 2004 (considered as one warning) and February 2005	-Low-strength risperidone use among pensioners decreased from 95,000 DDDs per month before the 2004 warnings to 90,000 after. This dropped to 65,000 DDDs after the 2005 warning. No change was seen for high-dose risperidone use among pensioners which increased throughout the study. -Low-strength olanzapine use among pensioners decreased from 15,000 DDDs before the 2004 warnings to 9,000 DDDs within a year. No change was seen after the 2005 warning. High-dose olanzapine use increased steadily throughout the study.

**Abbreviations:** ACheEI: acetylcholinesterase inhibitor; AIFA: *Agenzia Italiana del Farmaco* (Italian Drug Agency); EGB: *Echantillon Généraliste de Bénéficiaires*; EMA: European Medicines Agency; DDD: defined daily dose; FDA: Food and Drug Administration; GEK: *Gmünder Ersatz Kasse*, a German nationwide health insurance company database; HSD-CSD-LPD: Health Search Database - Cegedim Strategic Data, Longitudinal Patient Database; MHRA: Medicines and Healthcare Products Regulatory Agency; PCCIU: Primary Care Clinical Information Unit.

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**Appendix 2: Dementia diagnoses in THIN (UK) and HSD (Italy).**

<b>Dementia Read codes</b>	A410.00, A411.00, E00..00, E00..11, E00..12, E000.00, E001.00, E001000, E001100, E001200, E001300, E001z00, E002.00, E002000, E002100, E002z00, E003.00, E004.00, E004.11, E004000, E004100, E004200, E004300, E004z00, E012.00, E012.11, E012000, Eu00.00, Eu00000, Eu00011, Eu00012, Eu00013, Eu00100, Eu00111, Eu00112, Eu00113, Eu00200, Eu00z00, Eu00z11, Eu01000, Eu01200, Eu01300, Eu01y00, Eu01z00, Eu02000, Eu02100, Eu02400, Eu02z00, Eu02z11, Eu02z12, Eu02z13, Eu02z14, Eu02z15, Eu02z16, F110.00, F111.00, F116.00, F11x700, F21y200, F21y211, Fyu3000
<b>ICD9-CM dementia codes</b>	290, 290.0, 290.1, 290.10, 290.11, 290.12, 290.13, 290.2, 290.21, 290.20, 290.3, 290.4, 290.40, 290.41, 290.42, 290.43, 290.8, 290.9, 294.1, 331.0, 331.1

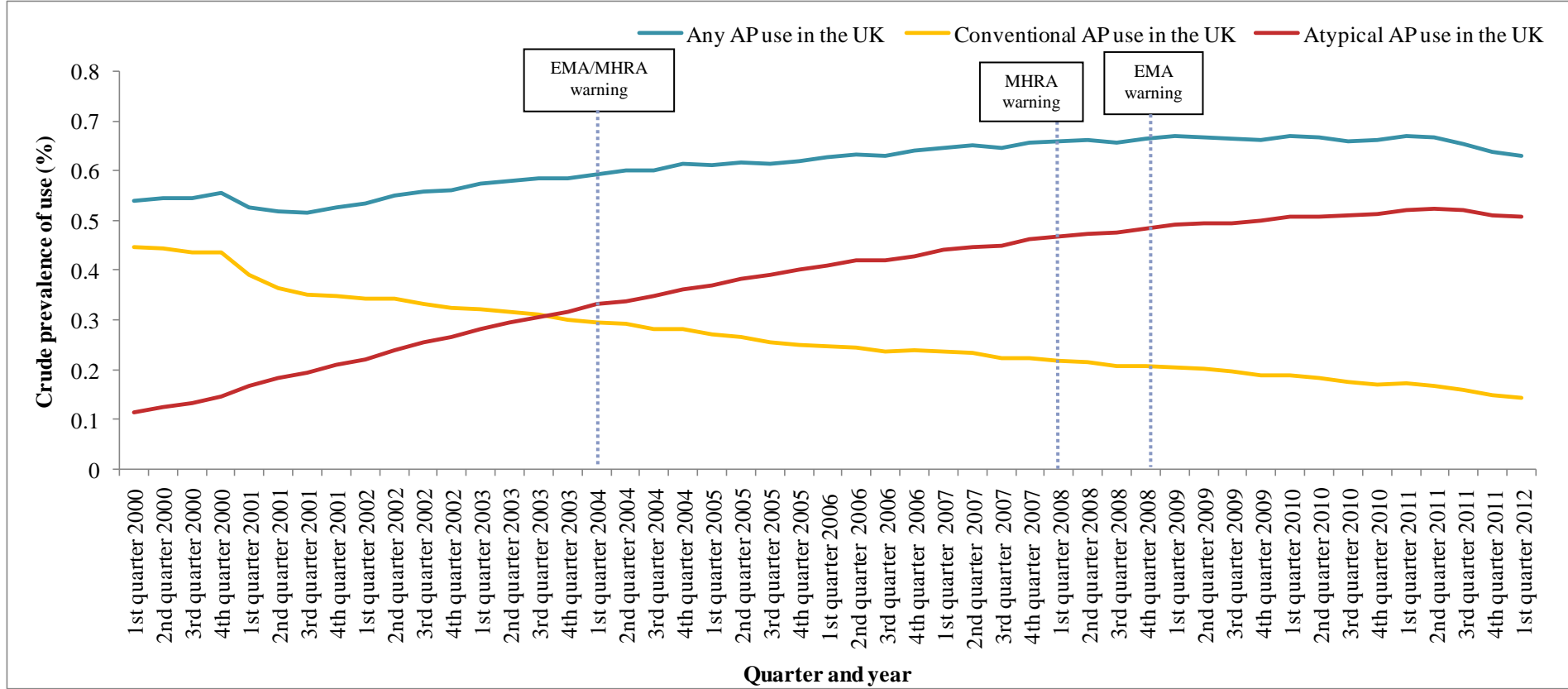
**Abbreviations:** ICD9-CM- international classification of diseases with clinical modification

**Appendix 3: Multilex codes for antipsychotic drugs in THIN (UK). All antipsychotics have the BNF code ‘4020100’.**

Drug name	Multilex Code
Amisulpride	91077998, 91425998, 88383997, 88383996, 88383998, 90209998, 86433998, 91083998, 94545990, 94845990, 88387997, 94544990, 94844990, 88387996, 88387998, 94846990
Aripiprazole	85834998, 87450998, 85833998, 87449998, 85832998, 87448998, 87089998, 83903998, 85835998, 85837998, 85836998, 87453998, 87452998, 87451998, 87090998
Benperidol	82225998, 88885998, 95979998, 95980998
Chlorpromazine	97871998, 82892998, 96689996, 97879998, 95200992, 97877998, 97880998, 97134992, 96689998, 97880997, 93242998, 97132992, 96689997, 97880996, 97129992, 96614992, 94111992, 94821992, 96102992, 94107992, 98186990, 96690998, 96691996, 99007990, 93587998, 93593998, 98062989, 95687990, 96690996, 98062990, 96690997, 96691997, 96919989, 97236988, 98192989, 96691998, 94761998, 95365990, 97236990, 98189990, 98192988, 94761997, 95364990, 96919990, 97236989, 98192990, 99010990
Chlorprothixene	96686997
Clozapine	87019998, 87340998, 93596997, 82800998, 87020998, 87341998, 93596998, 82802998, 82799998, 93595997, 82801998, 93595998, 82803998
Dartalan (Thiopropazate)	94891992
Droperidol	97343998, 97343997, 93674998, 97334992, 93675998, 96303997, 96303998
Flupenthixol	98766998, 98766997, 99775998, 97516998, 99776998, 86421998, 86420998, 85613998, 96502997, 96502998, 86422998, 96502996, 85614998, 94879998, 86423998, 96503998
Fluphenazine	85300998, 96342992, 85295998, 98759998, 85294998, 85299998, 85298998, 99414998, 93032992, 96498997, 96498998, 85296998, 85303998, 85302998, 96286990, 96742990, 85297998, 85301998, 99408998, 96500998, 99411998, 99411997, 99411996, 97466992, 96501998, 96501997, 96501996
Fluspirilene	99189998, 96494998
Haldoperidol	95086992, 96265992, 97946997, 96307992, 97344997, 97346997, 97945998, 97345997, 96242998, 97945997, 96758992, 97944997, 96242997, 97346996, 97945996, 97568992, 97946998, 96244998, 97344998, 97346998, 97946996, 83786998, 97944998, 96245997, 96245998, 96246998, 93695997, 83787998, 93695998, 98155990, 96247997, 96248996, 98131989, 98625989, 92815996, 96247998, 98625990, 91921998, 92815998, 98080990, 96247996, 98625988, 92815997, 96115990, 96249997, 97135989, 98131990, 8360988, 98544990, 96248998, 96248997, 96249998, 97135990, 96249996, 96889990, 98154990, 98544988
Levomepromazine	95918998, 98853997, 98853998, 95919998, 95919997, 82709998, 87504998, 87505998
Loxapine	94007998, 94007997, 94007996, 94006998, 94006997, 94006996
Olanzapine	91618997, 89569996, 91364998, 97433998, 90664998, 86324998, 85376998, 91618998, 89569998, 89569997, 90659996, 97995998, 86325998, 90659997, 87647998, 89567996, 7111998, 90659998, 85377998, 89567998, 89567997
Paliperidone	84524998, 84523998, 84527998, 84526998, 84525998
Pericyazine	83019998, 99362997, 98865998, 97878992, 83020998, 99362998, 99362996, 95576998, 95577997, 95577998, 95577996
Perphenazine	99651998, 99651997, 98587998, 97877992, 94164992, 95575998, 97786998, 97786997, 95575997, 95575996
Pimozide	97342996, 97342998, 97342997, 95516996, 95516998, 95516997
Pipotiazine	85409998, 98622998, 85410998, 85411998, 85413998, 95503998
Promazine	99117998, 98783998, 96750992, 93708997, 93708998, 97406989, 95385998, 95386998, 95386996, 95386997, 98063990, 95385997, 98063989, 93476998, 98786996, 93477998, 98786998, 99093990, 93477997, 98786997, 99093988
Quetiapine	88734996, 81923998, 88733997, 83492998, 88733998, 88734998, 88734997, 83491998, 87907998, 83490998, 83493998, 81924998, 83995998, 83994998, 83993998, 83996998, 82773998, 82772998, 88737998, 88737996, 88736997, 88736998, 88737997, 87908998
Risperidone	86983998, 92023998, 90395998, 99649998, 93240997, 91676998, 92107998, 99649997, 92089998, 85039998, 96914992, 99649996, 85038998, 93240998, 89908998, 93240996, 99637997, 91374998, 90396998, 85042998, 85040998, 86984998, 92491990, 88164998, 88163998, 95519998, 91968998, 92957990, 98585998, 98585997, 98585996, 92953990, 99637998, 99637996
Sertindole	89809997, 89809996, 89809998, 89812997, 89812996, 89811998, 89812998
Sulpiride	90805998, 97176998, 98796998, 90158998, 98796997, 98149992, 95226997, 95226998, 97163990, 97858990, 97966990, 95226996, 97163989
Thiopropazate	98174992

Thiopropazine	96492992, 98173992
Thioridazine	99436998, 98899997, 99437998, 99437997, 98899998, 98899996, 99437996, 96570992, 92821997, 95173996, 95174996, 95174997, 95173997, 98403989, 95173998, 98003989, 98403990, 92821998, 95174998, 98404988, 95175998, 95175997, 97715990, 98003990, 98404990, 95175996, 97715989, 98003988, 98404989
Trifluoperazine	99108996, 99107998, 95607992, 99109998, 99107997, 99109996, 99108997, 98203992, 99109997, 98206992, 95119998, 99108998, 95118997, 95119996, 95118998, 92623996, 95118996, 92623997, 92623998, 98052989, 98400990, 95119997, 98052990, 87435998
Trifluoperidol	95116997, 98204992, 95116998, 95117998, 95117997
Zotepine	98190996, 98190998, 98190997, 99337996, 99337998, 99337997
Zuclopenthix Decanoate	85607998, 95071998, 85609998, 96628998, 96628997, 98767998
Zuclopenthixol Acetate	93519998, 86332998, 86334998, 86333998, 86335998, 93520998
Zuclopenthixol Dihydrochloride	99821997, 99821996, 99821998, 96629997, 96629996, 96629998

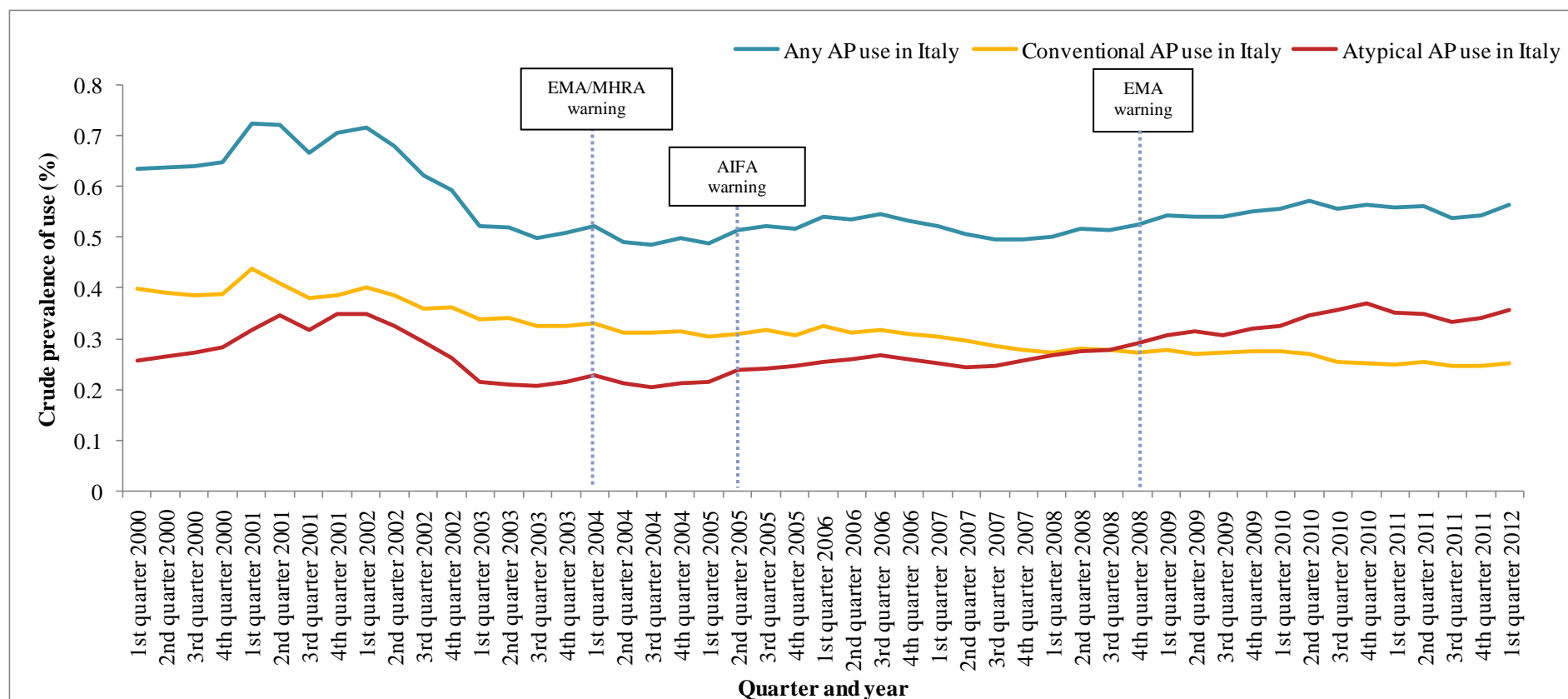
Appendix 4: Crude prevalence of antipsychotic use in patients under 65 years in the UK (THIN) per quarter year during the study period from the 1st quarter of 2000 to the 1st quarter of 2012, with main warnings labelled.



Abbreviations: AP- Antipsychotic; EMA- European Medicines Agency; MHRA- Medicines and Healthcare Products Regulatory Agency

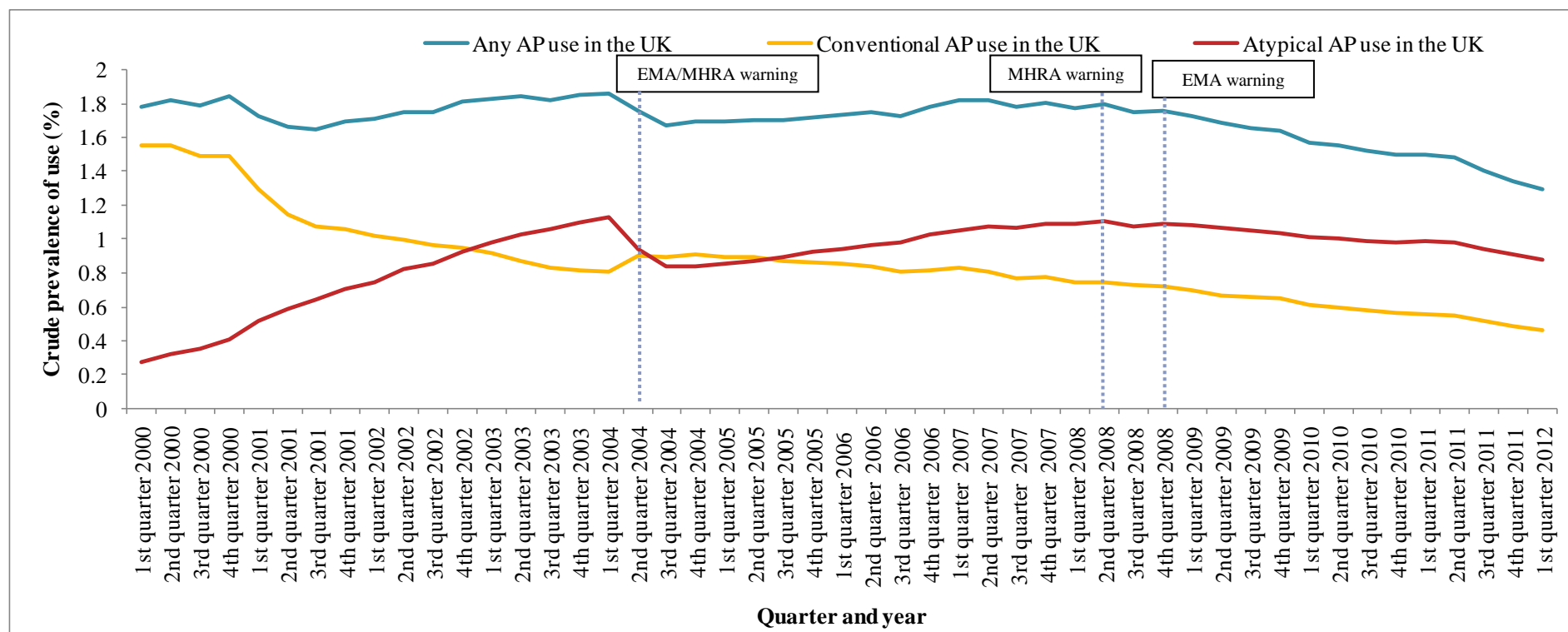


**Appendix 5: Crude prevalence of antipsychotic use in patients under 65 years per quarter year in Italy (HSD-CSD-LPD) from the 1st quarter of 2000 to the 1st quarter of 2012, with main warnings labelled.**



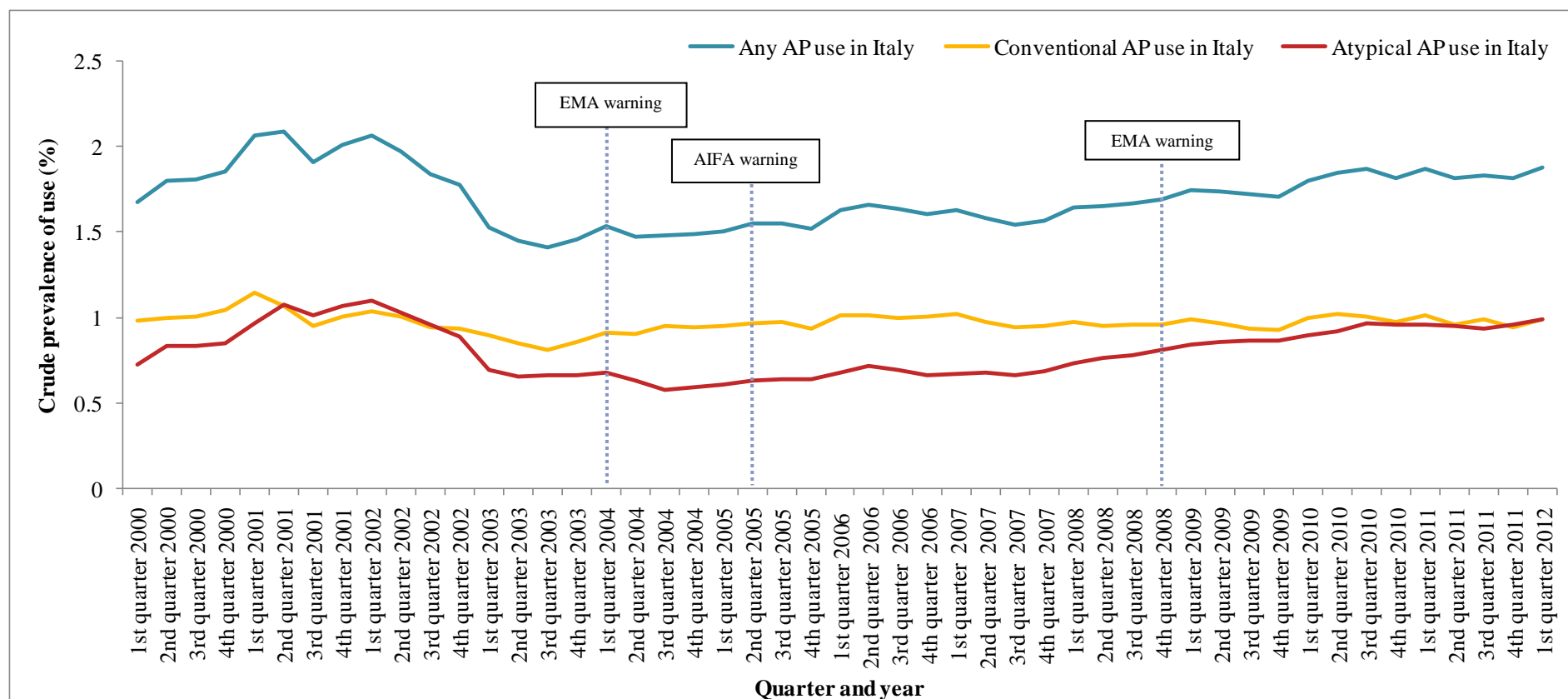
**Abbreviations:** AP- Antipsychotic; AIFA- Agenzia Italiana del Farmaco; EMA- European Medicines Agency

**Appendix 6: Crude prevalence of antipsychotic use in patients  $\geq 65$  years (irrespective of dementia diagnosis) per quarter year in the UK (THIN) from the 1st quarter of 2000 to the 1st quarter of 2012, with main warnings labelled.**



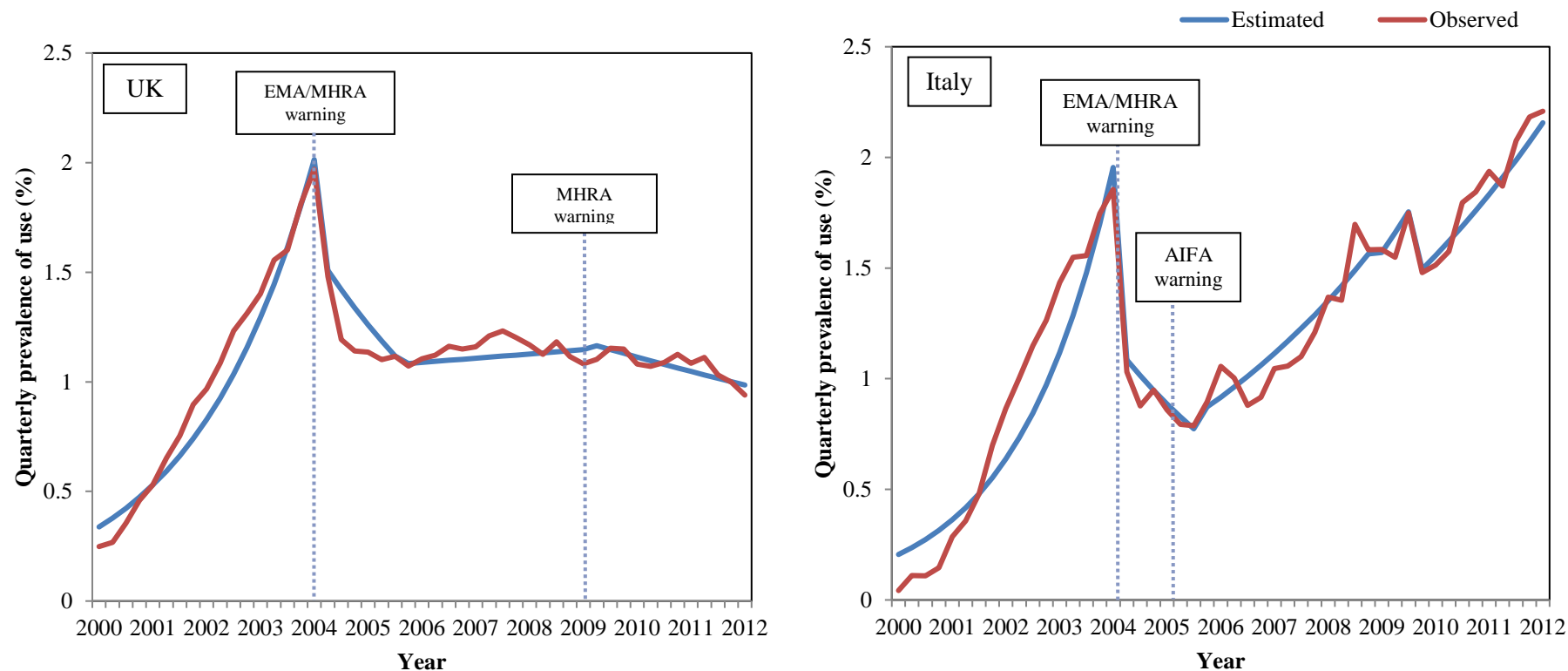
**Abbreviations:** AP- Antipsychotic; EMA- European Medicines Agency; MHRA- Medicines and Healthcare Products Regulatory Agency

**Appendix 7: Crude prevalence of antipsychotic use in patients  $\geq 65$  years (irrespective of dementia diagnosis) per quarter year in Italy (HSD-CSD-LPD) from the 1st quarter of 2000 to the 1st quarter of 2012, with main warnings labelled.**



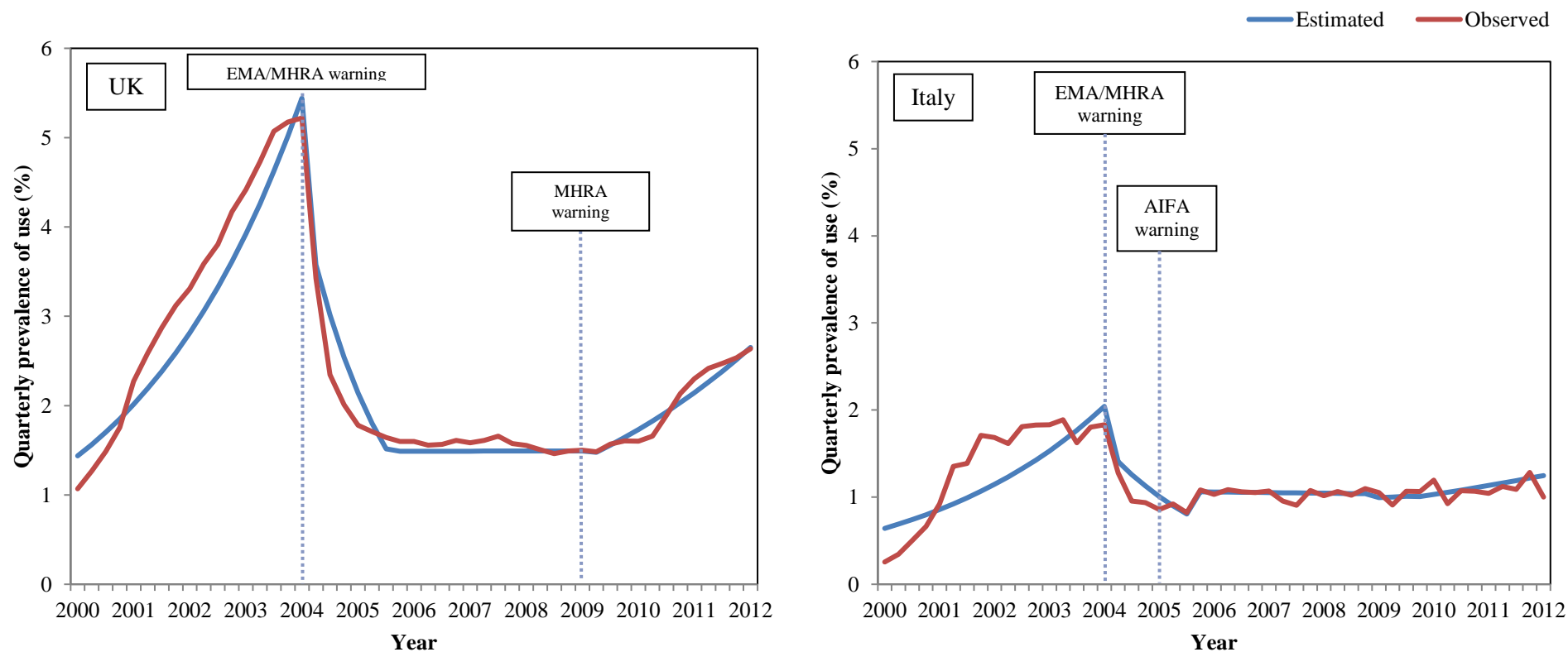
**Abbreviations:** AP- Antipsychotic; AIFA- Agenzia Italiana del Farmaco; EMA- European Medicines Agency

**Appendix 8: Quarterly prevalence rates of olanzapine use in dementia patients  $\geq 65$  years old in the UK (THIN- left panel) and Italy (HSD-CSD LPD- right panel) from the first quarter of 2000 to the first quarter of 2012, with main warnings labelled.**



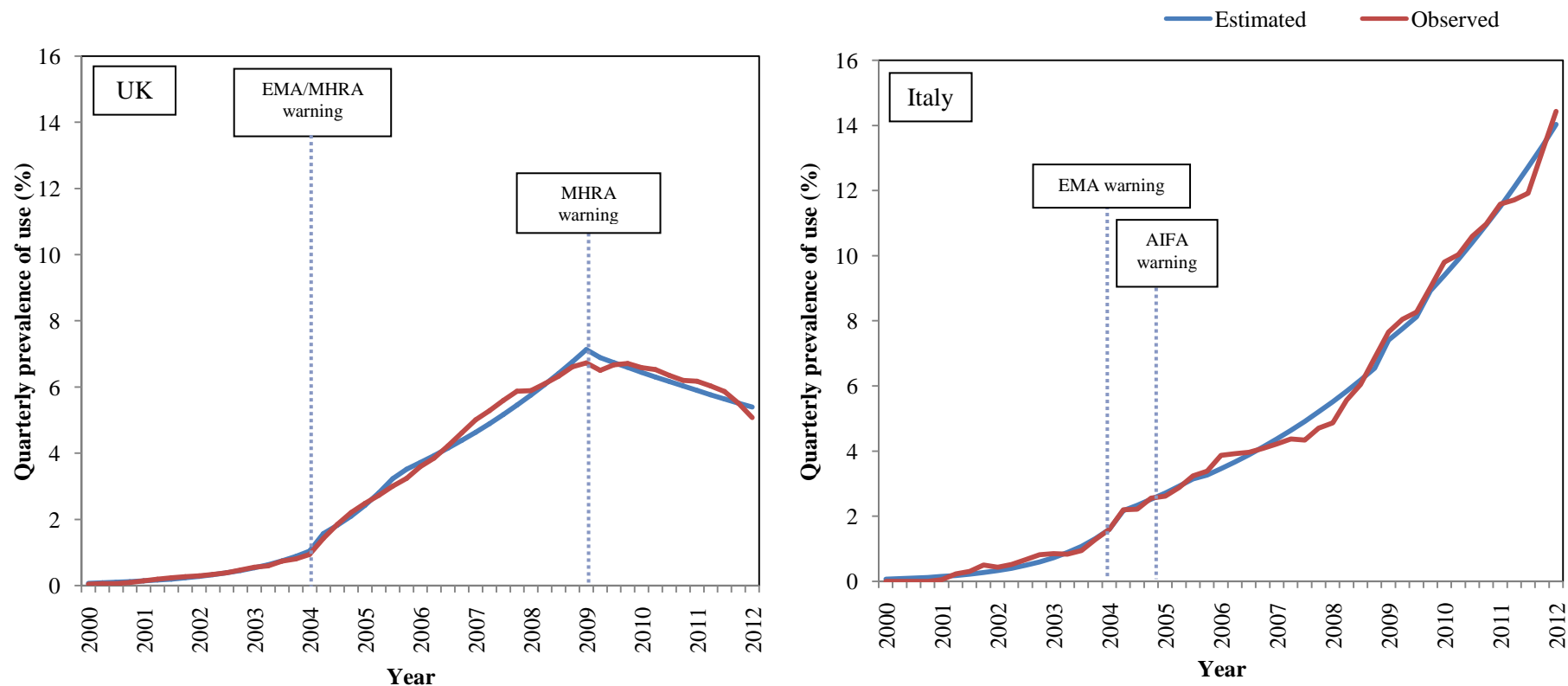
**Abbreviations:** AIFA- Agenzia Italiana del Farmaco; EMA- European Medicines Agency; MHRA- Medicines and Healthcare Products Regulatory Agency

**Appendix 9: Quarterly prevalence of risperidone use in dementia patients  $\geq 65$  years old in the UK (THIN- left panel) and Italy (HSD-CSD LPD -right panel) from the first quarter of 2000 to the first quarter of 2012, with main warnings labelled.**



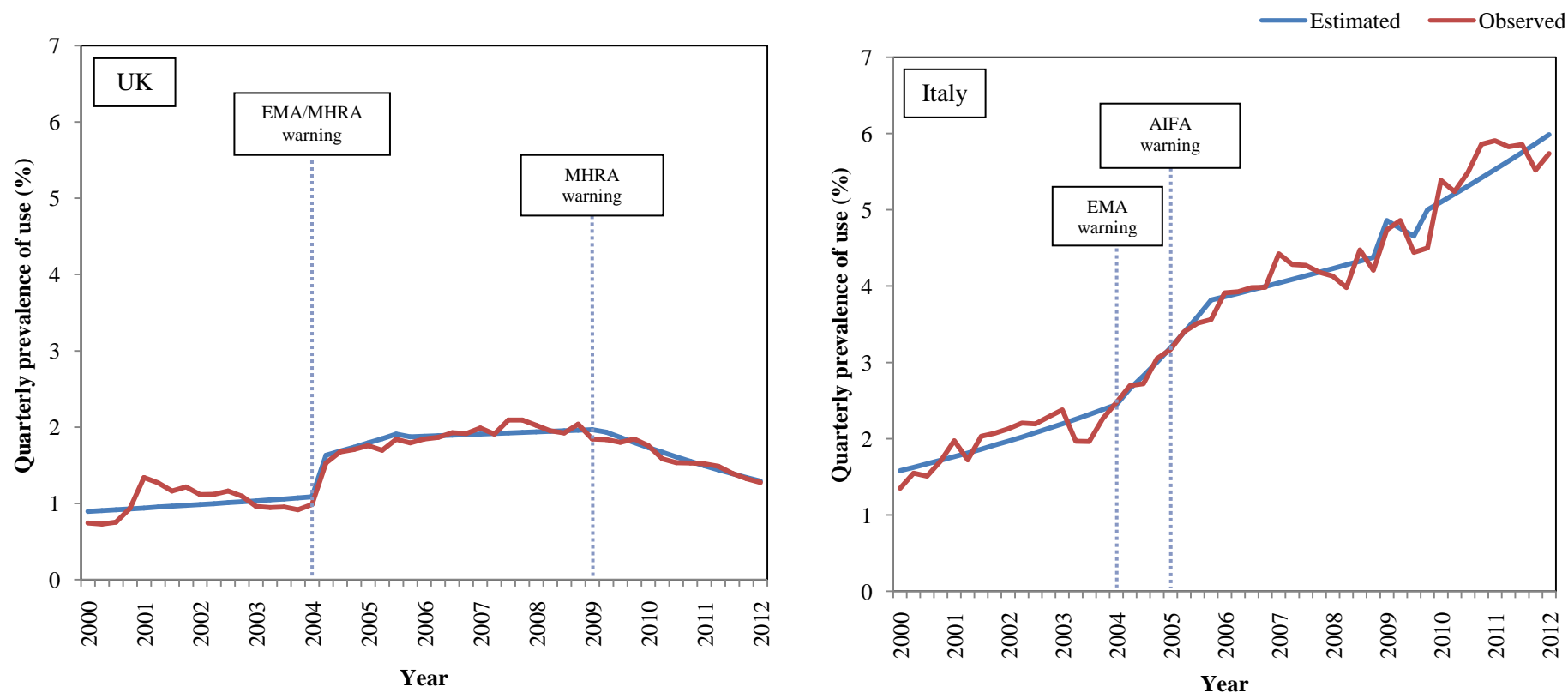
**Abbreviations:** AIFA- *Agenzia Italiana del Farmaco*; EMA- European Medicines Agency; MHRA- Medicines and Healthcare Products Regulatory Agency

**Appendix 10: Quarterly prevalence of quetiapine use in dementia patients  $\geq 65$  years old in the UK (THIN- left panel) and Italy (HSD-CSD LPD- right panel) from the first quarter of 2000 to the first quarter of 2012, with main warnings labelled.**



**Abbreviations:** AIFA- Agenzia Italiana del Farmaco; EMA- European Medicines Agency; MHRA- Medicines and Healthcare Products Regulatory Agency

**Appendix 11: Quarterly prevalence of haloperidol use in dementia patients  $\geq 65$  years old in the UK (THIN- left panel) and Italy (HSD-CSD LPD- right panel) from the first quarter of 2000 to the first quarter of 2012, with main warnings labelled.**



**Abbreviations:** AIFA- Agenzia Italiana del Farmaco; EMA- European Medicines Agency; MHRA- Medicines and Healthcare Products Regulatory Agency

**Appendix 11: Prevalence of antipsychotics use in patients 65 and over with dementia in the UK (THIN) at 3, 6 and 12 months before and after the warnings.**

Antipsychotic	Time window before and after warnings	Warning occurrence	Prevalence of AP use before the warning (%)	Prevalence of AP use after the warning (%)	Comparison between the prevalences (p-value)
Olanzapine	3 months	1 <sup>st</sup> quarter 2004	1.8	1.5	<0.001*
		1 <sup>st</sup> quarter 2009	1.1	1.1	0.893
	6 months	1 <sup>st</sup> quarter 2004	1.1	1.3	<0.001*
		1 <sup>st</sup> quarter 2009	1.1	1.1	0.756
	12 months	1 <sup>st</sup> quarter 2004	1.6	1.2	<0.001*
		1 <sup>st</sup> quarter 2009	1.1	1.1	0.573
Quetiapine	3 months	1 <sup>st</sup> quarter 2004	0.8	1.4	<0.001*
		1 <sup>st</sup> quarter 2009	6.6	6.5	0.612
	6 months	1 <sup>st</sup> quarter 2004	0.8	1.6	<0.001*
		1 <sup>st</sup> quarter 2009	6.5	6.6	0.457
	12 months	1 <sup>st</sup> quarter 2004	0.7	2.0	<0.001*
		1 <sup>st</sup> quarter 2009	6.2	6.6	<0.001*
Risperidone	3 months	1 <sup>st</sup> quarter 2004	5.2	3.4	<0.001*
		1 <sup>st</sup> quarter 2009	1.5	1.5	0.939
	6 months	1 <sup>st</sup> quarter 2004	5.1	2.9	<0.001*
		1 <sup>st</sup> quarter 2009	1.5	1.5	0.529
	12 months	1 <sup>st</sup> quarter 2004	4.9	2.4	<0.001*
		1 <sup>st</sup> quarter 2009	1.5	1.6	0.262
Haloperidol	3 months	1 <sup>st</sup> quarter 2004	0.9	1.5	<0.001*
		1 <sup>st</sup> quarter 2009	2.0	1.8	0.100
	6 months	1 <sup>st</sup> quarter 2004	0.9	1.6	<0.001*
		1 <sup>st</sup> quarter 2009	2.0	1.8	0.061
	12 months	1 <sup>st</sup> quarter 2004	0.9	1.7	<0.001*
		1 <sup>st</sup> quarter 2009	2.0	1.8	0.004*

\*Statistically significant (p-value <0.05). **Abbreviation:** AP- antipsychotic



**Appendix 12: Prevalence of antipsychotic use in patients 65 and over with dementia in Italy (HSD-CSD-LPD) at 3, 6 and 12 months before and after the warnings.**

Antipsychotic	Time window before and after warnings	Warning occurrence	Prevalence of AP use before warning (%)	Prevalence of AP use after warning (%)	Comparison between the two prevalences (p-value)
Olanzapine	3 months	1 <sup>st</sup> quarter 2004	1.7	1.0	<0.001*
		2 <sup>nd</sup> quarter 2009	1.6	1.7	0.460
	6 months	1 <sup>st</sup> quarter 2004	1.6	0.9	<0.001*
		2 <sup>nd</sup> quarter 2009	1.6	1.6	0.872
	12 months	1 <sup>st</sup> quarter 2004	1.6	0.9	<0.001*
		2 <sup>nd</sup> quarter 2009	1.5	1.6	0.808
Quetiapine	3 months	1 <sup>st</sup> quarter 2004	1.3	2.2	<0.001*
		2 <sup>nd</sup> quarter 2009	7.7	837	0.195
	6 months	1 <sup>st</sup> quarter 2004	1.1	2.2	<0.001*
		2 <sup>nd</sup> quarter 2009	7.3	8.6	<0.001*
	12 months	1 <sup>st</sup> quarter 2004	1.0	2.4	<0.001
		2 <sup>nd</sup> quarter 2009	6.5	9.3	<0.001*
Risperidone	3 months	1 <sup>st</sup> quarter 2004	1.8	1.3	0.005*
		2 <sup>nd</sup> quarter 2009	1.0	1.1	0.925
	6 months	1 <sup>st</sup> quarter 2004	1.7	1.1	<0.001*
		2 <sup>nd</sup> quarter 2009	1.1	1.1	0.952
	12 months	1 <sup>st</sup> quarter 2004	1.8	1.0	<0.001*
		2 <sup>nd</sup> quarter 2009	1.1	1.1	0.996
Haloperidol	3 months	1 <sup>st</sup> quarter 2004	2.3	2.7	0.066
		2 <sup>nd</sup> quarter 2009	4.7	4.4	0.417
	6 months	1 <sup>st</sup> quarter 2004	2.1	2.7	<0.001*
		2 <sup>nd</sup> quarter 2009	4.5	4.5	0.980
	12 months	1 <sup>st</sup> quarter 2004	2.1	3.0	<0.001*
		2 <sup>nd</sup> quarter 2009	4.3	4.9	0.003*

\*Statistically significant (p-value <0.05). **Abbreviation:** AP- antipsychotic

**Appendix 13: Median change in prevalence of antipsychotic use, along with 2.5 and 97.5 percentiles, for each quarter year in each time window in elderly people in the UK with dementia.**

		Start of study (1 <sup>st</sup> quarter 2000) to first EMA/MHRA warning (1 <sup>st</sup> quarter 2004)	First EMA/MHRA warning (1 <sup>st</sup> quarter 2004) to second EMA warning (3 <sup>rd</sup> quarter 2005)	Second EMA warning (3 <sup>rd</sup> quarter 2005) to second MHRA warning (1 <sup>st</sup> quarter 2009)	Second MHRA warning (1 <sup>st</sup> quarter 2009) to end of study (1 <sup>st</sup> quarter 2012)
Median changes in prevalence (%) per quarter year	All APs	0.0044% (-0.018, 0.241%)*	0.0016% (-0.005, 0.196%)*	0.0013% (-0.005, 0.337%)*	-0.0017% (-0.197, 0.002%)*
	Conventional APs	0.0042% (-0.228, 0.241%)*	0.0020% (-0.005, 0.196%)*	0.0007% (-0.019, 0.330%)*	-0.0019% (-0.197, 0.002%)*
	Atypical APs	0.0044% (-0.220, 0.513%)*	0.0024% (-0.005, 0.196%)*	0.0013% (-0.019, 0.350%)*	-0.0041% (-0.197, 0.002%)*
	Olanzapine	0.0055% (-0.220, 0.513%)*	0.0020% (-0.083, 0.196%)*	0.0039% (-0.019, 0.350%)*	-0.0071% (-0.195, 0.002%)*
	Quetiapine	0.0071% (-0.220, 0.513%)*	0.0024% (-0.083, 0.374%)*	0.0040% (-0.019, 0.352%)*	-0.0078% (-0.195, 0.002%)*
	Risperidone	0.0093% (-0.211, 0.470%)*	0.0020% (-0.475, 0.374%)*	0.0039% (-0.019, 0.352%)*	-0.0071% (-0.195, 0.117%)*
	Haloperidol	0.0110% (-0.211, 0.470%)*	0.0024% (-0.402, 0.325%)*	0.0040% (-0.019, 0.352%)*	-0.0078% (-0.195, 0.117%)*

\*The corresponding log odds ratio change of AP use for each unitary increase of a quarter year (test for linear trend) was statistically significant. The percentiles reported in brackets cannot be interpreted as the conventional 95% confidence intervals. **Abbreviations:** APs- antipsychotics; MHRA- Medicines and Healthcare Products Regulatory Agency; EMA: European Medicines Agency

**Appendix 14: Estimated annual prevalence rate in each time window in elderly people in the UK with dementia.**

		Start of study (1 <sup>st</sup> quarter 2000) to first EMA/MHRA warning (1 <sup>st</sup> quarter 2004)	First EMA/MHRA warning (1 <sup>st</sup> quarter 2004) to second EMA warning (3 <sup>rd</sup> quarter 2005)	Second EMA warning (3 <sup>rd</sup> quarter 2005) to second MHRA warning (1 <sup>st</sup> quarter 2009)	Second MHRA warning (1 <sup>st</sup> quarter 2009) to end of study (1 <sup>st</sup> quarter 2012)
Annual prevalence rate in person-years (%)	All APs	4.5%	8.4%	7.1%	8.7%
	Conventional APs	2.2%	3.6%	2.6%	2.5%
	Atypical APs	2.4%	5.2%	4.8%	6.5%
	Olanzapine	0.5%	1.1%	0.5%	0.6%
	Quetiapine	0.2%	1.6%	2.8%	3.8%
	Risperidone	0.0%	0.0%	0.1%	0.2%
	Haloperidol	1.7%	2.2%	0.9%	1.3%

**Abbreviations:** APs- antipsychotics; MHRA- Medicines and Healthcare Products Regulatory Agency; EMA- European Medicines Agency

**Appendix 15: Median change in prevalence of antipsychotic use, along with 2.5 and 97.5 percentiles, for each quarter year in each time window in Italian elderly people with dementia.**

		Start of study (1 <sup>st</sup> quarter 2000) to EMA warning (1 <sup>st</sup> quarter 2004)	EMA warning (1 <sup>st</sup> quarter 2004) to AIFA warning (3 <sup>rd</sup> quarter 2005)	AIFA warning (3 <sup>rd</sup> quarter 2005) to EMA/AIFA warning (4 <sup>th</sup> quarter 2008)	EMA/AIFA warning (4 <sup>th</sup> quarter 2008) to AIFA warning (3 <sup>rd</sup> quarter 2009)	AIFA warning (3 <sup>rd</sup> quarter 2009) to end of study (4 <sup>th</sup> quarter 2012)
Median changes in prevalence (%) per quarter year	All APs	0.0009% (-0.017, 0.182%)*	0.0014% (-0.008, 0.398%)*	0.0015% (-0.004, 0.433%)*	0.0011% (-0.017, 0.115%)	0.0005% (-0.005, 1.118%)*
	Conventional APs	0.0008% (-0.017, 0.179%)	0.0015% (-0.008, 0.398%)*	0.0016% (-0.004, 0.423%)*	0.0011% (-0.023, 0.013%)	0.0005% (-0.005, 1.118%)*
	Atypical APs	0.0009% (-0.017, 0.198%)*	0.0015% (-0.008, 0.398%)*	0.0018% (-0.004, 0.423%)*	0.0011% (-0.023, 0.219%)*	0.0008% (-0.005, 1.089%)*
	Olanzapine	0.0010% (-0.017, 0.201%)*	0.0015% (-0.054, 0.386%)*	0.0019% (-0.004, 0.423%)*	0.0011% (-0.023, 0.219%)	0.0012% (-0.005, 1.089%)*
	Quetiapine	0.0012% (-0.017, 0.204%)*	0.0015% (-0.054, 0.386%)*	0.0022% (-0.004, 0.423%)*	0.0011% (-0.023, 0.366%)*	0.0017% (-0.005, 1.089%)*
	Risperidone	0.0014% (-0.017, 0.204%)*	0.0015% (-0.095, 0.386%)*	0.0019% (-0.004, 0.414%)	0.0012% (-0.023, 0.366%)	0.0020% (-0.005, 1.060%)
	Haloperidol	0.0017% (-0.017, 0.203%)*	0.0015% (-0.095, 0.386%)*	0.0022% (-0.004, 0.414%)*	0.0011% (-0.104, 0.366%)	0.0020% (-0.005, 1.060%)*

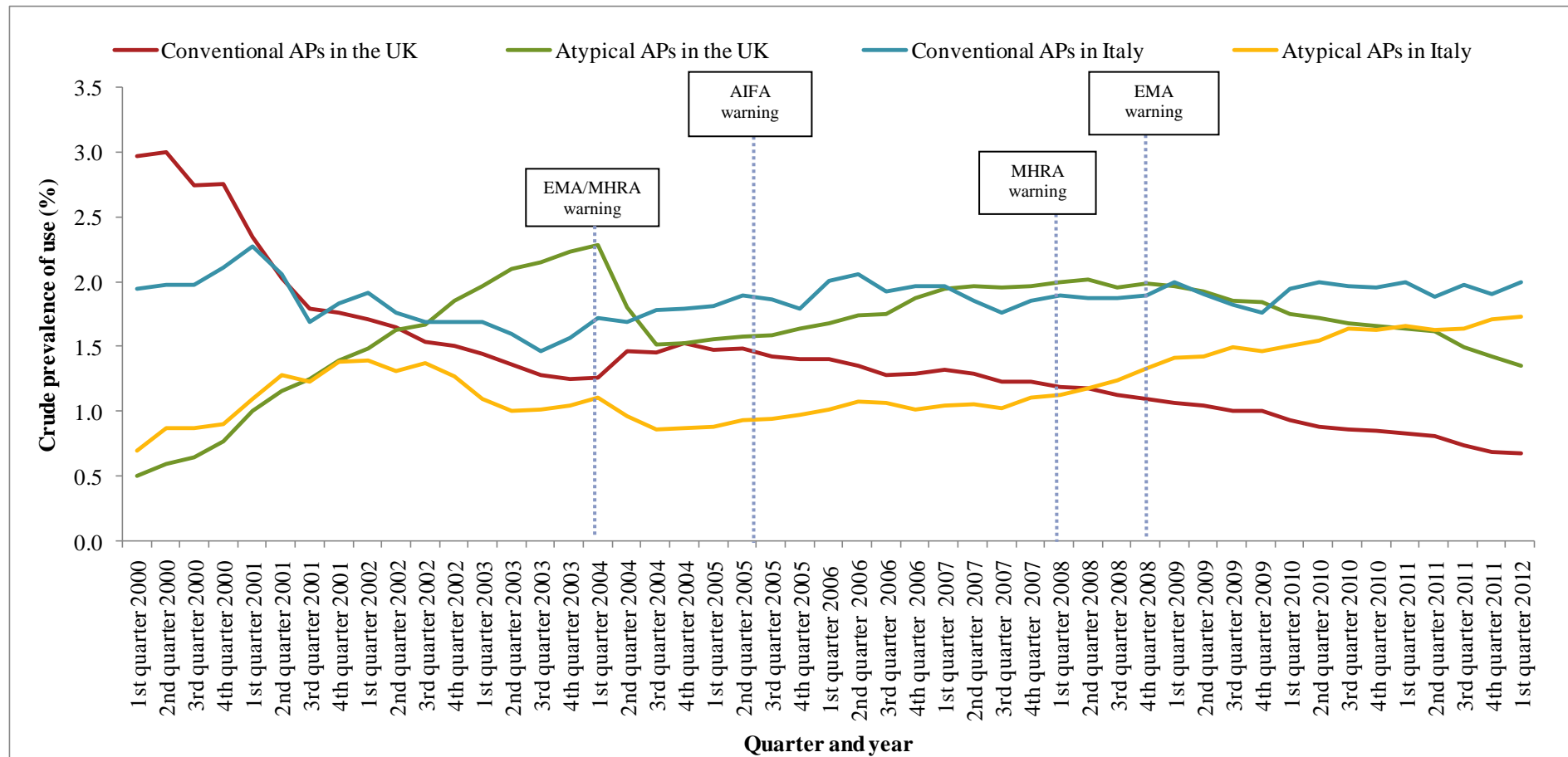
\*The corresponding log odds ratio change of AP use for each unitary increase of a quarter year (test for linear trend) was statistically significant. The percentiles reported in brackets cannot be interpreted as the conventional 95% confidence intervals. **Abbreviations:** AIFA- *Agenzia Italiana del Farmaco*; APs- antipsychotics; EMA- European Medicines Agency

**Appendix 16: Estimated annual prevalence rate in each time window in Italian elderly people with dementia.**

		Start of study (1 <sup>st</sup> quarter 2000) to EMA warning (1 <sup>st</sup> quarter 2004)	EMA warning (1 <sup>st</sup> quarter 2004) to AIFA warning (3 <sup>rd</sup> quarter 2005)	AIFA warning (3 <sup>rd</sup> quarter 2005) to EMA/AIFA warning (4 <sup>th</sup> quarter 2008)	EMA/AIFA warning (4 <sup>th</sup> quarter 2008) to AIFA warning (3 <sup>rd</sup> quarter 2009)	AIFA warning (3 <sup>rd</sup> quarter 2009) to end of study (4 <sup>th</sup> quarter 2012)
Annual prevalence rate in person-years (%)	All APs	3.9%	8.1%	6.3%	21.9%	11.5%
	Conventional APs	2.4%	4.8%	3.7%	11.1%	5.7%
	Atypical APs	1.7%	3.7%	3.0%	12.4%	6.6%
	Olanzapine	0.3%	0.7%	0.4%	1.6%	0.7%
	Quetiapine	0.2%	1.7%	1.8%	8.6%	4.9%
	Risperidone	0.0%	0.0%	0.0%	0.0%	0.0%
	Haloperidol	0.5%	0.8%	0.4%	1.1%	0.5%

**Abbreviations:** AIFA- *Agenzia Italiana del Farmaco*; APs- antipsychotics; EMA- European Medicines Agency

**Appendix 17: Prevalence of use of conventional and atypical antipsychotic use in patients  $\geq 80$  per quarter year in the UK (THIN) and Italy (HSD-CSD-LPD) year during the study period from the 1st quarter of 2000 to the 1st quarter of 2012.**



**Abbreviations:** AIFA- Agenzia Italiana del Farmaco; EMA- European Medicines Agency; MHRA- Medicines and Healthcare Products Regulatory Agency

**Appendix 18: Yearly prevalence of dementia in THIN in persons aged  $\geq 65$  years old (UK).**

Year	Numerator	Denominator	Prevalence of dementia (95% CI)
2000	3,616	916,087	0.4 (0.39-0.41)
2001	4,985	984,875	0.5 (0.49-0.51)
2002	6,457	1,059,397	0.6 (0.59-0.61)
2003	8,153	1,134,980	0.7 (0.68-0.72)
2004	10,095	1,211,921	0.8 (0.78-0.82)
2005	11,922	1,287,350	0.9 (0.88-0.92)
2006	14,077	1,364,504	1 (0.98-1.02)
2007	15,986	1,450,876	1.1 (1.08-1.12)
2008	17,878	1,539,736	1.2 (1.18-1.22)
2009	19,874	1,636,149	1.2 (1.18-1.22)
2010	21,833	1,728,766	1.3 (1.28-1.32)
2011	23,721	1,839,240	1.3 (1.28-1.32)

**Abbreviation:** 95% CI- 95% confidence intervals

**Appendix 19: Yearly prevalence of dementia in HSD-CSD-LPD in persons aged  $\geq 65$  years old (Italy).**

Year	Numerator	Denominator	Prevalence of dementia (95% CI)
2000	1,558	639,586	0.2 (0.19-0.21)
2001	2,180	721,107	0.3 (0.29-0.31)
2001	2,841	811,929	0.3 (0.29-0.31)
2003	3,335	871,157	0.4 (0.39-0.41)
2004	3,849	895,588	0.4 (0.39-0.41)
2005	4,348	907,515	0.5 (0.49-0.51)
2006	4,727	923,875	0.5 (0.49-0.51)
2007	5,032	938,065	0.5 (0.49-0.51)
2008	5,281	940,408	0.6 (0.58- 0.62)
2009	5,471	944,122	0.6 (0.58- 0.62)
2010	5,718	948,496	0.6 (0.58-0.62)
2011	5,519	944,784	0.6 (0.58-0.62)

**Abbreviation:** 95% CI- 95% confidence intervals